

## ORIGINAL RESEARCH ARTICLE

# Shared and specific susceptibility loci for schizophrenia and bipolar disorder: a dense genome scan in Eastern Quebec families

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The goal of this study was to identify susceptibility loci shared by schizophrenia (SZ) and bipolar disorder (BP), or specific to each. To this end, we performed a dense genome scan in a first sample of 21 multigenerational families of Eastern Quebec affected by SZ, BP or both ( $N = 480$  family members). This probably constitutes the first genome scan of SZ and BP that used the same ascertainment, statistical and molecular methods for the concurrent study of the two disorders. We genotyped 607 microsatellite markers of which 350 were spaced by 10 cM and 257 others were follow-up markers in positive regions at the 10 cM scan. Lander and Kruglyak thresholds were conservatively adjusted for multiple testings. We maximized the lod scores (mod score) over eight combinations (2 phenotype severity levels  $\times$  2 models of transmission  $\times$  2 analyses, affected/unaffected vs affected-only). We observed five genome-wide significant linkages with mod score  $> 4.0$ : three for BP (15q11.1, 16p12.3, 18q12–q21) and two for the shared phenotype, that is, the common locus (CL) phenotype (15q26, 18q12–q21). Nine mod scores exceeded the suggestive threshold of 2.6: three for BP (3q21, 10p13, 12q23), three for SZ (6p22, 13q13, 18q21) and three for the CL phenotype (2q12.3, 13q14, 16p13). Mod scores  $> 1.9$  might represent confirmatory linkages of formerly reported genomewide significant findings such as our finding in 6p22.3 for SZ. Several regions appeared to be shared by SZ and BP. One linkage signal (15q26) appeared novel, whereas others overlapped formerly reported susceptibility regions. Despite the methodological limitations we raised, our data support the following trends: (i) results from several genome scans of SZ and BP in different populations tend to converge in specific genomic regions and (ii) some of these susceptibility regions may be shared by SZ and BP, whereas others may be specific to each. The present results support the relevance of investigating concurrently SZ and BP within the same study and have implications for the modelling of genetic effects.

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Family, twin and adoption studies have shown that schizophrenia (SZ) and bipolar disorder (BP) are complex and highly heritable disorders. SZ and BP share the features of other complex genetic disorders such as incomplete penetrance, non-Mendelian inheritance, heterogeneity and probable phenocopies.<sup>1–6</sup> Linkage studies have proven successful in detecting susceptibility genes for complex disorders such as Alzheimer's disease, breast cancer, colon cancer and diabetes. Recent findings in psychiatric genetics have renewed enthusiasm. For SZ, the available evidence

from published genome scans and recent review papers<sup>7–10</sup> supports converging chromosomal regions as including probable loci for susceptibility genes: 1q21–q22, 6p24–p22, 8p21, 10p15–p11, 13q32 and 22q11–q13 showed up as the most congruent across SZ studies. As regards BP, several scans and reviews of linkage studies<sup>5,10–12</sup> also conclude to converging susceptibility regions, the most likely being in 4p16–p15, 12q23, 13q32, 16p, 18q12–q22, 21q22 and 22q11–q12.

While most recent genome scans suggest multiple gene effects for SZ and BP,<sup>6,10</sup> some studies highlighted the possibility of major gene effects for SZ in subsets of families. In a sample of large Eastern Canadian SZ families, Brzustowicz *et al*<sup>13</sup> observed under parametric linkage analysis a lod score of 6.5 in chromosome 1q21–q22 under the assumption of heterogeneity. Lindholm *et al*<sup>14</sup> reported, in one very

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large SZ pedigree of Sweden, a lod score of 6.6 in 6q25.2 and described a 6 cM haplotype in this region segregating with the disorder. However, we<sup>15</sup> and others,<sup>16–22</sup> as well as a meta-analysis,<sup>23</sup> reported negative results in 1q21–q22, whereas two studies<sup>24,25</sup> provided confirmations.

From the beginning of our research program, we implemented the concurrent study of SZ and BP in order to test our hypothesis that some susceptibility genes might be shared by SZ and BP, whereas others would be specific to each disorder.<sup>26,27</sup> This decision was motivated (i) by family studies suggesting some degree of familial coaggregation of SZ and BP<sup>4,28–30</sup> and (ii) the need to preserve total blindness to the predominant diagnosis in an SZ or a BP pedigree to avoid a diagnostic bias that we showed as significantly affecting diagnostic accuracy.<sup>31</sup> Two other sets of findings support this SZ/BP commonality. First, we were among the first to demonstrate, by means of factor analysis, that the dimensional model of Liddle crossed diagnostic boundaries and was common to SZ and BP,<sup>27</sup> which has been confirmed in other populations.<sup>32–35</sup> Second, this conceptualization was also supported by findings from our first-stage genome scan, in which we reported a linkage in 18q21.1 that was potentially shared by both SZ and BP.<sup>36</sup> These findings are consistent with those of other groups, which provided evidence of shared SZ/BP loci on chromosomes 3, 10, 13, 18 and 22.<sup>16,37–42</sup>

In summary, four main observations can be made from recent linkage studies of SZ or BP and reviews:<sup>5,7–12,37</sup> (i) few genome scans studied concurrently SZ and BP with the same methods; (ii) emerging findings seem to converge in around 12–15 regions of the genome for the two disorders; (iii) an increasing number of linkage findings formerly apparent in only one major psychosis now appears as likely related to both SZ and BP and (iv) most of the published genome scans of SZ and BP report one or two linkages that meet accepted statistical thresholds such as those of Lander and Kruglyak.<sup>43</sup> The latter observation renders more difficult the investigation of interplays, additive or interactive, between susceptibility loci to explain the expression of the two syndromes.

This paper reports on a full genome scan, more precisely on the second stage of a two-stage genome scan in our first sample of 480 family members (sample 1). A first stage in 13 candidate chromosomal regions was formerly published in this journal.<sup>36</sup> The present article reports on the complete and denser scan of the genome (stage II) together with the results of stage I. Stage I had shown one genomewide significant linkage in 18q12 ( $Z=4.03$ ) for BP and possibly also related to SZ, and one potential confirmatory finding in 6p24–p22 ( $Z_{het}=3.47$ ,  $\alpha=0.66$ ) for SZ.<sup>36</sup>

## Methods

### Sample and ascertainment

All the subjects signed a written consent after they were personally explained the study by an investi-

gator. The ascertainment, diagnostic methods and reliability have been described in detail in previous reports.<sup>15,26,31,36</sup> Briefly, information from an interview with the subjects (Structured Clinical Interview for DSM-III-R), from relatives and from the lifetime medical records, was gathered. Based on this information, a consensus best-estimate DSM-III-R diagnosis (BED) was derived by a panel of four research psychiatrists who were blind to diagnoses in relatives.

We selected, in the Eastern Quebec population, the families with the following criteria: (i) at least one first-degree relative affected with the same disorder as the proband, that is, affected by SZ if the proband was affected by SZ or by BP if the proband was affected by BP, and (ii) at least two additional first-, second- or third-degree relatives affected by the proband's disorder. In all, we required at least four affected members per family including the proband. We selected 21 families: six had 30–50 members, five had 20–29, seven had 10–20 and three had less than 10 family members. Finally, the families had an average number of six members affected by SZ or BP. The sample consisted of seven SZ pedigrees (at least 85% of ill members affected by SZ or an SZ spectrum disorder, the remaining 15% having a BP spectrum disorder), six BP pedigrees (at least 85% of ill members affected by BP or a BP spectrum disorder, the remaining 15% having an SZ spectrum disorder) and eight mixed pedigrees, that is, affected almost equally by both major psychoses. Such a rate of mixed pedigrees may have resulted from our using a blind BED. We indeed reported data showing that, in case of disagreements between diagnosticians, unblind best-estimate diagnoses tended to be in continuity with the most predominant diagnosis of the pedigree more frequently than blind diagnoses.<sup>26,31</sup> However, other studies using similar methods did not find high rates of mixed pedigrees. One cannot eliminate the possibility that the observation of such mixed pedigrees be a particularity of the Eastern Quebec population. Another possibility is that the size of our families may explain the mixture of some pedigrees: the larger the family, the more likely it can become mixed. Altogether, DNA was available from 480 family members. In all, 47 deceased ancestors for whom a diagnosis could be made, but from whom DNA was not available, were also included in the linkage analyses.

The mean age of onset was 25.4 (SD = 8.5) years for SZ and 28.8 (SD = 10.3) years for BP. The mean current age was 43.8 and 56.4 years, respectively. Males constituted 46% of the broad CL phenotype definition.

### Phenotype definitions

The narrow SZ phenotype was restricted to SZ diagnosis ( $N=71$ ), and the broad phenotype included SZ, schizopreniform and schizotypal personality disorders ( $N=81$ ). The narrow BP phenotype was restricted to BP I ( $N=48$ ) and the broad phenotype included BP I, BP II and recurrent major depression

( $N=72$ ). To test the hypothesis that some susceptibility loci may be shared by SZ and BP, we used a common locus (CL) phenotype definition that combined the SZ and BP phenotypes: the narrow CL phenotype included SZ, BP I and schizoaffective disorder (SZA) ( $N=134$ ), while the broad CL phenotype included the CL narrow, plus recurrent major depression, schizophreniform and schizotypal personality disorders ( $N=169$ ). Although included in the CL phenotype, SZA was excluded from the SZ and the BP phenotype definitions given that family studies are ambiguous about the specificity of the coaggregation with SZ or BP.

The SZ, BP and CL phenotype definitions were analyzed regardless of the pedigree categorization in SZ, BP or mixed pedigrees. An SZ pedigree had no power for the analysis of the BP phenotype and conversely a BP pedigree had no power for the analysis of the SZ phenotype. When the BP phenotypes were analyzed, the SZ phenotypes were treated as 'unaffected' in the analysis using the affecteds and the unaffecteds, and as 'unknown' in the affected-only analysis. When the SZ phenotypes were under analysis, the BP phenotypes were treated as 'unaffected' in the affected/unaffected analysis, and as 'unknown' in the affected-only analysis.

#### Genotyping

The DNA polymorphisms used were highly informative di-, tri- and tetranucleotide microsatellite repeats for which PCR primers were synthesized (Alpha DNA, Montreal) after adding an M13 tail to the forward primer. A semiautomated genotyping procedure using laser infrared automatic DNA sequencers, and automated genotyping software (SAGA) from LICOR were used.<sup>44</sup>

Microsatellite genotypes were called automatically using the SAGA software. After automatic genotyping, which was read blind to the phenotypes, manual editing of the results was performed when needed. Results were then stored in a local database where Mendelian inheritance was checked using the computer software PedCheck.<sup>45</sup> Subjects who failed the Mendelian test were reanalyzed completely, that is, from the PCR to the genotyping. The completed genome scan in sample 1 comprised 607 markers (ie 350 markers in a 10 cM resolution map plus 257 additional markers to follow-up on regions showing a  $Z > 1.9$ ).

#### Linkage analyses

Model-based (or parametric) linkage analyses were performed since they are more powerful than model-free (or nonparametric) analyses,<sup>46</sup> even when the mode of inheritance specified is only approximately correct, provided that at least one dominant and one recessive model are considered.<sup>47</sup> Two- and three-point lod scores were systematically computed using the FASTLINK version of the LINKAGE programs.<sup>48</sup> Markers have been located according to the Genetic

Location Database (LDB; <http://cedar.genetics.soton.ac.uk>).

For each of our diagnostic classes, we used a narrow and a broad phenotype definition. We used two transmission models, one dominant and one recessive, which both modelled a disease gene with reduced penetrance. The dominant model assumed a disease allele frequency of 0.01, a cumulative penetrance at high age of 0.70 and a phenocopy rate of 0.20. The parameter values for the recessive model were respectively 0.10, 0.70 and 0.10. Both models specified age-dependent penetrance and took into account the certainty of diagnosis by increasing the phenocopy rate in liability classes corresponding to probable and possible diagnoses, as suggested by Ott.<sup>49</sup> All these analyses were first carried out using both affected and unaffected subjects, and then using affected-only to reduce the impact of a misspecification in the penetrance parameters. The exact penetrance values of the two models can be found in Maziade *et al.*<sup>15</sup>

For each of our three diagnostic classes (SZ, BP and CL), we obtained a mod score by maximizing the lod score (termed Zmax; maximized over the recombination fraction) over the eight possible combinations resulting from (i) the two levels of stringency in phenotype definitions (narrow vs broad); (ii) two different transmission models (dominant vs recessive) and (iii) two different types of analyses (affected/unaffected analysis vs affected-only analysis).

Although using a mod score approach yields a greater power to detect linkage than using a single model,<sup>50</sup> it will inevitably inflate the rate of type I error. Hence, although we relied mainly on Lander and Kruglyak<sup>43</sup> Z criteria to assess the genomewide significance level, we also corrected for multiple testing. To do so, we raised our Z criteria for level of significance by 0.70, following the guidelines of Hodge *et al.*<sup>51</sup> which is rather conservative since the 24 analyses per marker (3 diagnostic classes  $\times$  8 combinations) were not all independent due to the considerable overlap in phenotype definitions. Therefore, our adjusted Z criteria were 4.0 for a *significant* linkage, 2.6 for a *suggestive* linkage, and we used 1.9 for a linkage signal or *confirmatory* linkage only in regions where 'significant' linkage was previously reported (Lander and Kruglyak criterion).<sup>43</sup> Three-point analyses were systematically performed using pairs of adjacent markers plus the disease locus. Hence, each marker was included in two three-point analyses, one for each flanking marker. Linkage analyses under the assumption of heterogeneity were performed using the admixture model implemented in the HOMOG program<sup>52</sup> for the two- and three-point mod scores exceeding the 1.9 threshold.

Power was assessed by simulations with SLINK and MSIM. Assuming genetic homogeneity and a recombination fraction ( $\theta$ ) of 0.05, the expected lod scores ranged from 8.6 to 21.8 depending on the phenotype definition and the mode of inheritance used, and power exceeded 98%. Assuming a  $\theta$  of 0.05 and a

proportion of linked families ( $\alpha$ ) of 0.7, the expected lod scores under genetic heterogeneity (ELOD<sub>HET</sub>) ranged from 4.9 to 11.3 and power ranged from 66 to 93%. The ELOD<sub>HET</sub> and power for  $\theta = 0.05$  and  $\alpha = 0.5$  ranged respectively from 3.06 to 6.7 and from 43 to 72%.

## Results

The two-point mod score curves for each diagnostic class (SZ, BP and CL) are shown in Figure 1, providing the level of affection (either narrow or broad) for which the highest mod score was obtained for a given chromosome. The results meeting our criterion for confirmatory linkage ( $Z \geq 1.9$ ) either in two- or three-point analysis are reported in Table 1. When several markers within 25 cM met this criterion for the same phenotype definition, only the marker showing the strongest mod score was included in Table 1 as an attempt to obtain a set of independent results.

For the *BP phenotypes*, three mod scores exceeded our adjusted genomewide significant threshold of 4.0: 15q11.1 ( $Z = 4.59$  at D15S122), 18q12.3 ( $Z = 4.10$  at D18S1145) and 16p12.3 ( $Z = 4.05$  at D16S410). We also found three suggestive linkages with mod scores above 2.6 in 12q23.1 ( $Z = 3.53$ ), 3q21.2 ( $Z = 2.68$ ) and 10p13 ( $Z = 2.66$ ). With the *SZ phenotypes*, no genomewide significant findings were found but three loci showed suggestive mod scores  $> 2.6$ . At 6p22.3, we had a mod of 2.82 and a  $Z_{het}$  of 3.47 (D6S334;  $\alpha = 0.66$ ,  $P = 0.06$ ), a result we had reported in our stage 1 scan.<sup>36</sup> The two other suggestive linkages ( $Z = 3.87$  and 2.96) were respectively observed in 18q21.1 (D18S851) and 13q13.3 (D13S1491). With the *shared phenotypes* (CL), we obtained two genomewide significant linkages, one in 18q21.1 ( $Z = 4.46$  at D18S472) and the other in 15q26 ( $Z = 4.55$  at D15S1014). Three other signals reached the suggestive threshold in 16p13.1 ( $Z = 3.66$  at D16S3041), 2q22.1 ( $Z = 2.76$  at D2S298) and 13q14.1 ( $Z = 2.74$  at D13S1247). Results in Table 2 show that no mod scores in the sample resulted from the contribution of only one or very few pedigrees. Whether or not some of our suggestive ( $> 2.6$ ) or linkage signals ( $> 1.9$ ) meet the confirmatory threshold depends on the presence and interpretation of a formerly reported genomewide significant finding at the same site with a similar phenotype. This is addressed in Discussion.

## Discussion

Prior to discussing our results, the following limitations have to be considered. First, we adopted thresholds that were adjusted for multiple testings. The question as to whether these criteria apply to a small subset of large families is still open. Also, whether or not these criteria apply to a two-step procedure consisting of a sparse genome scan (10 cM) followed by dense genotyping of the positive regions

is unclear and difficult to address through simulations.

Second, the sensitivity of heterogeneity tests for linkage analyses, performed in samples that include a small number of large families, has not been well studied so far. Hence, the linkage results herein reported may have failed to detect between-family heterogeneity. We plan to follow-up on these results by studying linkage evidence in individual families given the power of each pedigree.

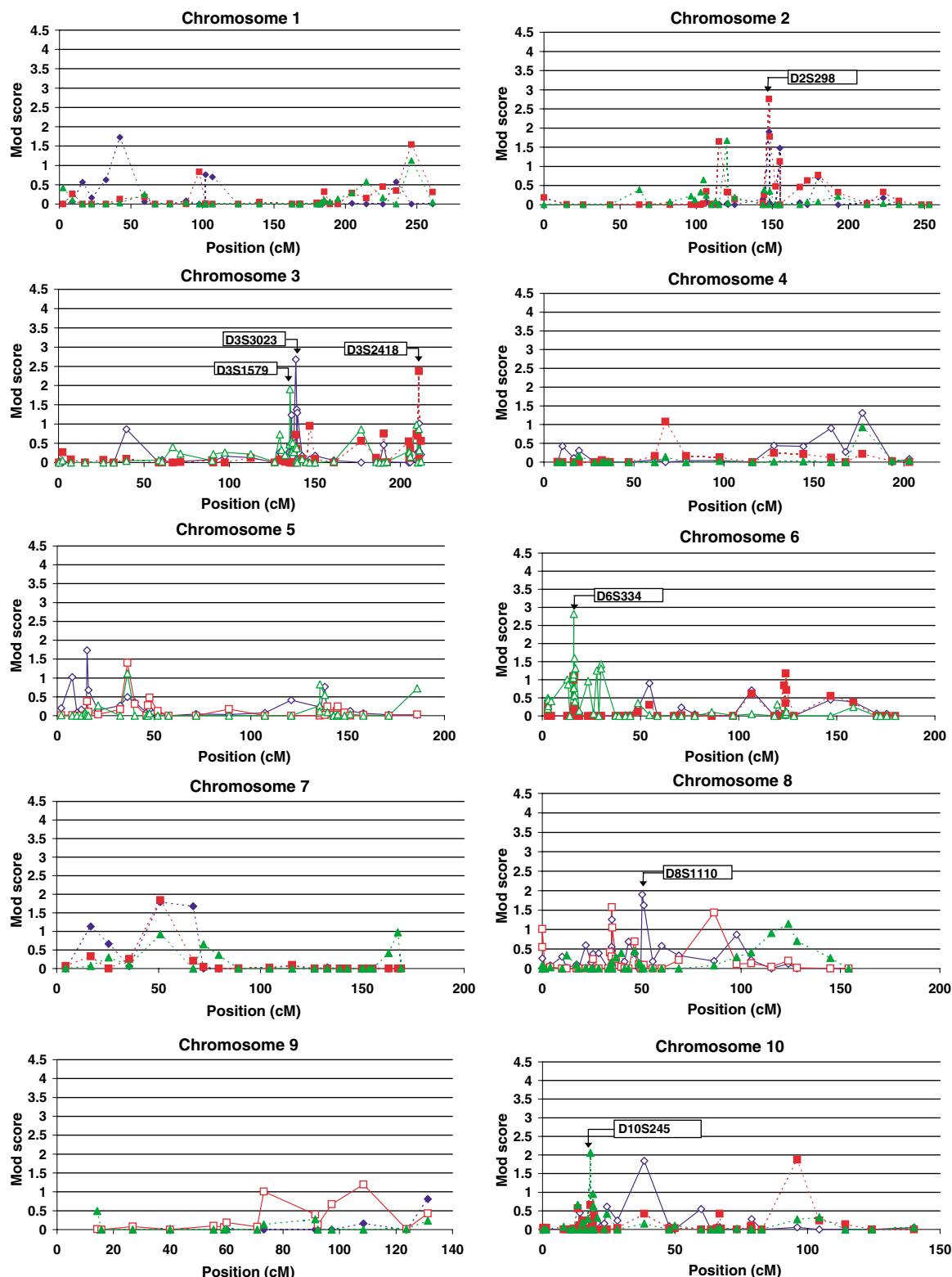
Third, the issue of replication in linkage studies is complex. Indeed, studies vary in terms of sampling, diagnostic and statistical methods as well as in terms of the genetic markers used.<sup>53,54</sup> It is then difficult to determine the extent to which linkage signals reported in the same chromosomal area in different studies represent a true replication.

Bearing in mind the above considerations, we will discuss chromosome by chromosome our positive findings in terms of (i) their interpretation based on the adjusted statistical thresholds of Lander and Kruglyak;<sup>43</sup> (ii) the specific or shared characteristics of a susceptibility region with respect to SZ and BP and (iii) their potential congruency with the converging linkage regions emerging from the published genome scans. Tables 1 and 2 summarize our linkage signals reaching the significant or suggestive thresholds, whereas Table 3 shows our results in comparison with the main findings of others in a particular chromosomal region.

### Genomewide significant linkage findings

**Chromosome 15q** A significant linkage in 15q26.3 was observed with the CL phenotype, that is, a mod score of 4.55 with the multipoint analysis involving D15S1014 and D15S966. As shown in Figure 1, marker D15S657, located 0.63 cM centromeric to D15S1014, yielded a mod score of 2.31 for BP and marker D15S1014 gave 2.31 for the SZ phenotype. This finding appears to be novel. Another significant peak of 4.59 on chromosome 15, located around 80 cM from the precedent, was observed in 15q11 with the broad BP phenotype (marker D15S122) in the multipoint analysis with the affected-only analysis. In that region, a strong linkage signal has already been observed with the P50 sensory gating deficit phenotype in an SZ family.<sup>55</sup> As also shown in Table 3, a significant linkage has also been reported in BP probands with a good response to lithium and their relatives affected by either BP, recurrent major depression or SZA.<sup>56</sup> It is difficult to interpret, at this moment, whether there is one or several susceptibility genes in 15q11, for SZ, BP or both (Table 3).

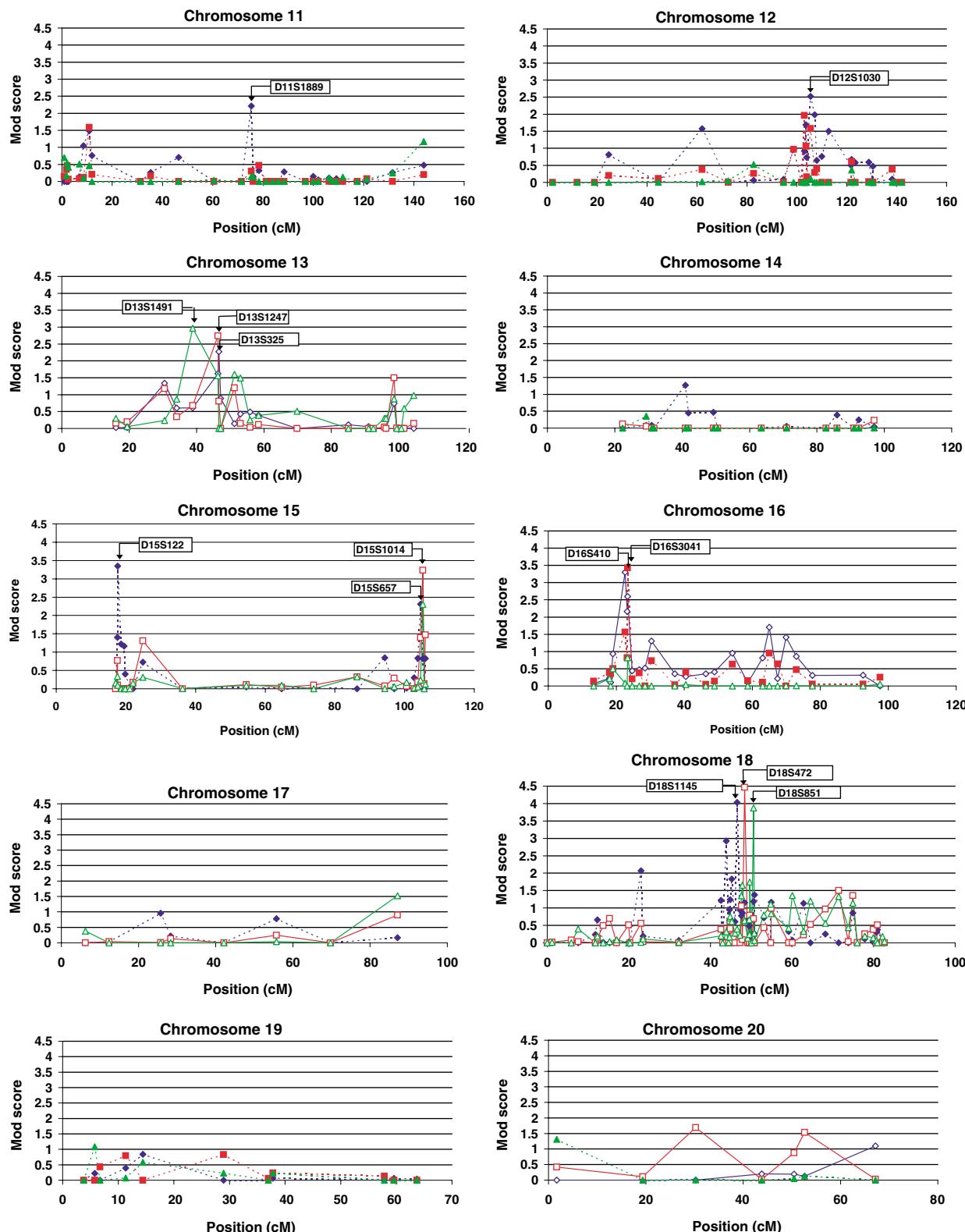
**Chromosome 16p** A genomewide significant finding was obtained on chromosome 16p12.3 with a mod of 4.05 by the multipoint analysis with D16S410–D16S403 and the BP phenotype. We also



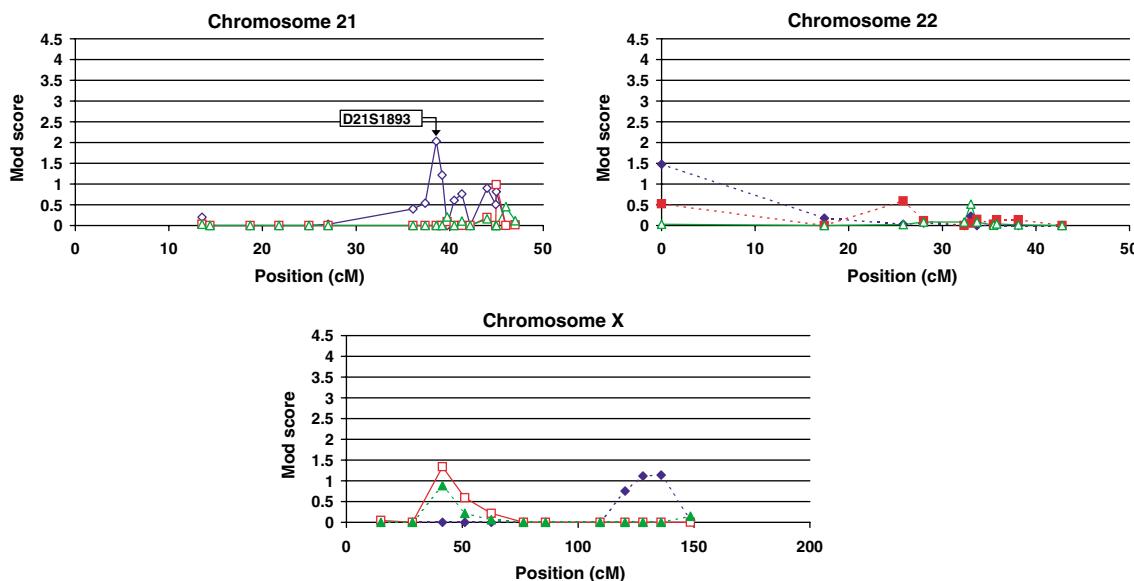
**Figure 1** Mod score curves (two-point) for the 23 pairs of chromosomes involving 607 markers covering the whole genome. For each diagnostic hierarchy (SZ, BP and CL), we provided the level of affection (either narrow or broad) for which the highest mod score was obtained for a given chromosome. The narrow bipolar phenotype is represented by clear diamonds and a full line in blue ( $\diamond$ — $\diamond$ ), and the broad bipolar phenotype by solid diamonds and a dashed line in blue ( $\blacklozenge$ ··· $\blacklozenge$ ). The narrow SZ phenotype is represented by clear triangles and a full line in green ( $\triangle$ — $\triangle$ ), and the broad SZ phenotype by solid triangles and a dashed line in green ( $\blacktriangle$ ··· $\blacktriangle$ ). The narrow common loci phenotype is represented by clear squares and a full line in red ( $\square$ — $\square$ ), and the broad common loci phenotype by solid squares and a dashed line in red ( $\blacksquare$ ··· $\blacksquare$ ).

obtained a multipoint mod score of 3.66 with the shared CL phenotype just 1 cM away, at D16S3041. One would expect that when the CL phenotype yields

a signal, such as here, both the BP and the SZ phenotypes should also yield a signal, but the SZ phenotype offered no signal as shown in Figure 1 and



**Figure 1** continued.

**Figure 1** continued.**Table 1** Chromosomal regions with mod scores meeting significant ( $Z \geq 4.0$ ) or suggestive ( $Z \geq 2.6$ ) thresholds

| Chr   | Region       | Marker   | Map (cM) | Phenotype     | Mode of inheritance <sup>a</sup> | Mod score <sup>b,c</sup> (θ)                |
|---|--------------|----------|----------|---------------|----------------------------------|---|
| <i>Genomewide significant linkage (<math>\geq 4.0</math>)</i> |              |          |          |               |                                  |   |
| 15  | q11.1        | D15S122  | 17.6     | BP broad      | D-ao                             | <b>4.59<sup>M</sup> (0.00)</b>              |
|   | q26.3        | D15S1014 | 105.2    | SZ, CL narrow | R-ao, R-au                       | 2.31 (0.05), <b>4.55<sup>M</sup> (0.20)</b> |
|   |              | D15S657  | 104.6    | BP broad      | R-ao                             | 2.31 (0.05)                                 |
| 16  | p12.3–p13.1  | D16S410  | 22.6     | BP narrow     | R-ao                             | <b>4.05<sup>M</sup> (0.00)</b>              |
|   |              | D16S3041 | 23.3     | CL broad      | R-ao                             | <b>3.66<sup>M</sup> (0.10)</b>              |
|   | q21          | D16S3253 | 65.0     | BP broad      | D-ao                             | 2.19 (0.01)                                 |
| 18  | q12.3–q21.1  | D18S1145 | 46.6     | BP broad      | R-au                             | <b>4.10<sup>M</sup> (0.20)</b>              |
|   |              | D18S472  | 48.4     | CL narrow     | R-ao                             | <b>4.46</b> (0.02)                          |
|   |              | D18S851  | 50.6     | SZ narrow     | D-au                             | <b>3.87</b> (0.10)                          |
| <i>Suggestive linkage (<math>\geq 2.6</math>)</i>             |              |          |          |               |                                  |   |
| 2   | q12.3–q22.1  | D2S121   | 114.9    | CL narrow     | R-ao                             | 2.18 (0.10)                                 |
|   |              | D2S298   | 147.8    | BP, CL broad  | D-ao                             | 1.91 (0.15), <b>2.76</b> (0.20)             |
| 3   | q21.1–q21.2  | D3S1579  | 135.4    | SZ narrow     | R-ao                             | 1.91 (0.05)                                 |
|   |              | D3S3023  | 138.9    | BP narrow     | D-ao                             | <b>2.68</b> (0.05)                          |
|   | q29          | D3S2418  | 210.9    | CL broad      | D-ao                             | 2.37 (0.25)                                 |
| 6   | p22.3        | D6S334   | 16.0     | SZ narrow     | D-ao                             | <b>2.82</b> (0.10)                          |
| 10  | p13          | D10S245  | 18.1     | SZ broad      | D-ao                             | 2.06 (0.15)                                 |
|   |              | D10S674  | 18.2     | BP narrow     | D-ao                             | <b>2.66<sup>M</sup> (0.00)</b>              |
| 12  | q23.1        | D12S332  | 103.0    | CL broad      | D-ao                             | 2.25 <sup>M</sup> (0.10)                    |
|   |              | D12S1030 | 105.5    | BP broad      | R-ao                             | <b>3.53<sup>M</sup> (0.09)</b>              |
| 13  | q13.3–q14.11 | D13S1491 | 38.9     | SZ narrow     | D-ao                             | <b>2.96</b> (0.05)                          |
|   |              | D13S1247 | 46.3     | CL narrow     | D-ao                             | <b>2.74</b> (0.15)                          |
|   |              | D13S325  | 46.6     | BP narrow     | D-ao                             | 2.27 (0.05)                                 |

<sup>a</sup>Modes of inheritance are either dominant (D) or recessive (R) and either affected-only (ao) or affected/unaffected (au).<sup>b</sup>The mod score was obtained with the two- or three-point (M) linkage analysis.<sup>c</sup>Mod scores meeting adjusted Lander and Kruglyak significant and suggestive thresholds are in bold characters.

Table 1. This is probably due to the presence of a few diagnoses other than SZ in families mainly affected by SZ, where the CL phenotype turned out to be more

informative than SZ. This 25–30 cM region is the site of findings for BP from several genome scans, as shown in Table 3.

**Table 2** Percentage of families according to their individual lod score contributing to the significant and suggestive total mod scores

| Marker                                | Mod score | Phenotype | Individual pedigree lod score interval |                 |                 |                 |           | Highest family lod score |
|---------------------------------------|-----------|-----------|--|-----------------|-----------------|-----------------|-----------|--------------------------|
|                                       |           |           | lod < 0.1                              | 0.1 ≤ lod < 0.4 | 0.4 ≤ lod < 0.8 | 0.8 ≤ lod < 1.2 | 1.2 ≤ lod |                          |
| <i>Genomewide significant linkage</i> |           |           |  |                 |                 |                 |           |                          |
| D15S122                               | 4.59      | BP broad  | 29%                                    | 21%             | 36%             | 14%             | 0%        | 1.04                     |
| D15S1014                              | 4.55      | CL narrow | 29%                                    | 48%             | 19%             | 0%              | 5%        | 1.22                     |
| D16S410                               | 4.05      | BP narrow | 21%                                    | 21%             | 57%             | 0%              | 0%        | 0.61                     |
| D16S3041                              | 3.66      | CL broad  | 33%                                    | 29%             | 38%             | 0%              | 0%        | 0.67                     |
| D18S1145                              | 4.10      | BP broad  | 43%                                    | 21%             | 21%             | 7%              | 7%        | 1.21                     |
| D18S472                               | 4.46      | CL narrow | 33%                                    | 43%             | 24%             | 0%              | 0%        | 0.71                     |
| D18S851                               | 3.87      | SZ narrow | 33%                                    | 53%             | 7%              | 0%              | 7%        | 2.03                     |
| <i>Suggestive linkage</i>             |           |           |  |                 |                 |                 |           |                          |
| D2S298                                | 2.76      | CL broad  | 52%                                    | 38%             | 5%              | 0%              | 5%        | 1.41                     |
| D3S3023                               | 2.68      | BP narrow | 57%                                    | 14%             | 21%             | 7%              | 0%        | 1.04                     |
| D6S334                                | 2.82      | SZ narrow | 40%                                    | 33%             | 7%              | 20%             | 0%        | 1.06                     |
| D10S674                               | 2.66      | BP narrow | 50%                                    | 7%              | 43%             | 0%              | 0%        | 0.79                     |
| D12S1030                              | 3.53      | BP broad  | 21%                                    | 57%             | 14%             | 7%              | 0%        | 0.81                     |
| D13S1491                              | 2.96      | SZ narrow | 33%                                    | 40%             | 13%             | 13%             | 0%        | 1.00                     |
| D13S1247                              | 2.74      | CL narrow | 57%                                    | 19%             | 14%             | 5%              | 5%        | 1.69                     |

For the analyses of the BP, the SZ and the CL phenotypes, the numbers of pedigrees under analysis were respectively 14, 15 and 21.

**Table 3** Comparison of present linkage findings to those of published genome scans of SZ or BP in other populations according to LDB map

| Location   | Marker   | LDB map (cM) | Lod or P-value       | Phenotype | References                       |
|------------|----------|--------------|----------------------|-----------|----------------------------------|
| 2p13–p12   | D2S441   | 69.0         | 3.20                 | BP        | Liu et al <sup>69</sup>          |
|            | D2S99    | 73.6         | 2.54                 | BP        | McInnis et al <sup>70</sup>      |
| 2q22.1     | D2S121   | 114.9        | 2.18                 | CL        | This study                       |
|            | D2S410   | 125.3        | 2.01                 | SZ        | Levinson et al <sup>71</sup>     |
|            | D2S298   | 147.8        | 2.76                 | CL        | This study                       |
|            |          | 138.1–149.6* | P < 0.05             | BP        | Segurado et al <sup>58</sup>     |
| 2q37.1     | D2S427   | 247.9        | 4.43                 | SZ        | Paunio et al <sup>72</sup>       |
| 3q21.2     | D3S1276  | 97.4         | 3.55 <sup>NPL</sup>  | BP        | Bailer et al <sup>42</sup>       |
|            | D3S1303  | 137.0        | 2.49 <sup>NPL</sup>  | BP        | Bailer et al <sup>42</sup>       |
|            | D3S3023  | 138.9        | 2.68                 | BP        | This study                       |
| 3q29       | D3S2418  | 210.9        | 2.37                 | CL        | This study                       |
|            | D3S1265  | 212.1        | 3.74 <sup>NPL</sup>  | SZ + BP   | Bailer et al <sup>42</sup>       |
| 6p22.3     | D6S7     | 0.8          | 2.47                 | BP        | Ginns et al <sup>63</sup>        |
|            | D6S296   | 3.1          | 3.51                 | SZ        | Straub et al <sup>59</sup>       |
|            | D6S334   | 16.0         | 3.47                 | SZ        | This study                       |
|            | D6S274   | 16.1         | P = 0.005            | SZ        | Moises et al <sup>73</sup>       |
|            | D6S274   | 16.1         | 4.19                 | SZ        | Turecki et al <sup>60</sup>      |
|            | D6S274   | 16.1         | 2.2                  | SZ        | Schwab et al <sup>21</sup>       |
| 8p22–p11.1 | D8S503   | 5.7          | P = 0.00006          | BP        | Ophoff et al <sup>66</sup>       |
|            | D8S1731  | 17.2         | 2.0                  | SZ        | Kendler et al <sup>74</sup>      |
|            | D8S1715  | 23.9         | 2.52                 | SZ        | Kendler et al <sup>74</sup>      |
|            | D8S136   | 25.5         | 3.49                 | SZ        | Brzustowicz et al <sup>75</sup>  |
|            | D8S1771  | 33.3         | 4.54 <sup>HLOD</sup> | SZ        | Blouin et al <sup>16</sup>       |
|            | D8S1771  | 33.3         | 5.04                 | SZ        | Pulver et al <sup>76</sup>       |
|            | D8S1771  | 33.3         | 3.2                  | SZ        | Gurling et al <sup>24</sup>      |
|            | —        | 33.3*        | P = 0.0001           | SZ + BP   | Badner and Gershon <sup>57</sup> |
|            | D8S532   | 48.6         | 3.06                 | SZ        | Stefansson et al <sup>77</sup>   |
|            | D8S1110  | 50.2         | 1.90                 | BP        | This study                       |
| 10p15–p11  | D10S245  | 18.0         | 2.06                 | SZ        | This study                       |
|            | D10S674  | 18.2         | 3.27                 | SZ        | Straub et al <sup>78</sup>       |
|            | D10S674  | 18.2         | 2.66 <sup>M</sup>    | BP        | This study                       |
|            | D10S1423 | 19.1         | 3.4 <sup>NPL</sup>   | SZ        | Faraone et al <sup>77</sup>      |

**Table 3** Continued

| Location      | Marker    | LDB map (cM) | Lod or P-value      | Phenotype | References                                 |
|---------------|-----------|--------------|---------------------|-----------|--|
| 10q22         | D10S1423  | 19.1         | 3.40                | BP        | Rice <i>et al</i> <sup>79</sup>            |
|               | D10S1423  | 19.1         | 2.5                 | BP        | Foroud <i>et al</i> <sup>39</sup>          |
|               | D10S1714  | 19.1         | 3.2 <sup>NPL</sup>  | SZ        | Schwab <i>et al</i> <sup>40</sup>          |
|               | D10S188   | 78.9         | 3.47                | BP        | Rice <i>et al</i> <sup>79</sup>            |
|               | D10S169   | 144.0        | 2.79                | BP        | Liu <i>et al</i> <sup>69</sup>             |
|               | D12S332   | 102.9        | 2.03                | BP        | This study                                 |
|               | D12S1030  | 105.5        | 3.53                | BP        | This study                                 |
|               | D12S82    | 129.3        | 3.9                 | BP        | Morissette <i>et al</i> <sup>80</sup>      |
|               | D12S1639  | 137.7        | 3.37                | BP        | Ewald <i>et al</i> <sup>81</sup>           |
|               | D12S97    | 142.2        | 2.43                | SZ + BP   | Bailer <i>et al</i> <sup>42</sup>          |
| 13q13.3–q14   | D13S1493  | 30.5         | 2.53                | BP        | McInnis <i>et al</i> <sup>70</sup>         |
|               | D13S1491  | 38.9         | 2.96                | SZ        | This study                                 |
|               | D13S1247  | 46.3         | 2.74                | CL        | This study                                 |
|               | D13S325   | 46.6         | 2.27                | BP        | This study                                 |
|               | D13S1272– | 51.2–55.5    | 4.09                | BP        | Badenhop <i>et al</i> <sup>65</sup>        |
|               | D13S153   |              |                     |           |  |
|               | D13S170   | 80.1         | 1.83                | SZ        | Shaw <i>et al</i> <sup>25</sup>            |
|               | D13S793   | 95.8         | 2.09                | SZ        | Brzustowicz <i>et al</i> <sup>75</sup>     |
|               | D13S1271– | 97.9–98.6    | 3.4                 | BP        | Detera-Wadleigh <i>et al</i> <sup>38</sup> |
|               | D13S779   |              |                     |           |  |
| 15q11.1       | —         | 98.0*        | P=0.00006           | BP        | Badner and Gershon <sup>57</sup>           |
|               | D13S779   | 98.6         | 2.2                 | BP        | Liu <i>et al</i> <sup>69</sup>             |
|               | D13S779   | 98.6         | 1.65                | SZ        | Maziade <i>et al</i> <sup>36</sup>         |
|               | D13S174   | 99.7         | 4.18 <sup>NPL</sup> | SZ        | Blouin <i>et al</i> <sup>16</sup>          |
|               | D13S796   | 104.5        | 2.34                | BP        | Kelsoe <i>et al</i> <sup>41</sup>          |
|               | D15S122   | 17.6         | 4.59                | BP        | This study                                 |
|               | D15S128   | 19.3         | 1.96 <sup>NPL</sup> | SZ        | Kauffman <sup>19</sup>                     |
|               | D15S1360  | 29.9         | 5.3                 | SZ/P50    | Freedman <i>et al</i> <sup>55</sup>        |
|               | D15S1043  | 38.4         | 1.79                | SZ        | Riley <i>et al</i> <sup>7</sup>            |
|               | ACTC      | 49.6         | 3.46                | BP        | Turecki <i>et al</i> <sup>56</sup>         |
| 15q26         | D15S1012  | 52           | 2.75                | SZ        | Stober <i>et al</i> <sup>82</sup>          |
|               | D15S657   | 104.6        | 2.31                | BP        | This study                                 |
|               | D15S1014  | 105.2        | 4.55                | CL        | This study                                 |
|               | D15S1014  | 105.2        | 2.31                | SZ        | This study                                 |
| 16p12.3       | D16S510   | 4.2          | 2.23                | BP        | Ewald <i>et al</i> <sup>83</sup>           |
|               | D16S749   | 8.3          | 2.8                 | BP        | Dick <i>et al</i> <sup>84</sup>            |
|               | D16S410   | 22.6         | 4.05 <sup>M</sup>   | BP        | This study                                 |
|               | D16S3041  | 23.3         | 3.66 <sup>M</sup>   | CL        | This study                                 |
|               | D16S749   | 24.8         | 1.7                 | BP        | Foroud <i>et al</i> <sup>39</sup>          |
|               | D16S769   | 37           | 3.4                 | BP        | Ekholm <i>et al</i> <sup>85</sup>          |
|               | D18S32    | 7.6          | P=0.000001          | BP        | Berrettini <i>et al</i> <sup>86</sup>      |
|               | D18S53    | 13.7         | 3.1                 | SZ        | Schwab <i>et al</i> <sup>87</sup>          |
| 18q12.3–q32   | —         | 5.4–44.4*    | P<0.05              | BP        | Segurado <i>et al</i> <sup>58</sup>        |
|               | D18S451   | 44.7         | 1.76                | SZ        | Williams <i>et al</i> <sup>22</sup>        |
|               | D18S1145  | 46.5         | 4.10                | BP        | This study                                 |
|               | D18S472   | 48.4         | 4.55                | CL        | This study                                 |
|               | D18S851   | 50.6         | 3.87                | SZ        | This study                                 |
|               | D18S41    | 54.8         | P=0.0004            | BP        | Stine <i>et al</i> <sup>88</sup>           |
|               | D18S878   | 73.8         | 2.90                | BP        | McInnis <i>et al</i> <sup>70</sup>         |
|               | D18S541–  | 70.0–71.1    | 5.42                | BP        | Schulze <i>et al</i> <sup>89</sup>         |
|               | D18S469   |              |                     |           |  |
|               | D18S70    | 82.7         | 4.06                | BP        | Freimer <i>et al</i> <sup>90</sup>         |
| 21q22.1–q22.3 | D21S1893  | 38           | 2.03                | BP        | This study                                 |
|               | D21S1260  | 39.8         | 3.35                | BP        | Aita <i>et al</i> <sup>67</sup>            |
|               | PFKL      | 42.5         | 3.41                | BP        | Straub <i>et al</i> <sup>91</sup>          |
|               | PFKL      | 42.5         | 2.04                | BP        | Kelsoe <i>et al</i> <sup>41</sup>          |
|               | —         | 34.2–49.5*   | P<0.05              | BP        | Segurado <sup>58</sup>                     |
|               | D21S212   | 49.0         | 1.79                | BP        | Detera-Wadleigh <i>et al</i> <sup>68</sup> |

CL: common locus phenotype; BP: bipolar phenotype; SZ: schizophrenia phenotype; NPL: nonparametric linkage; HLOD: heterogeneity lod score.

The symbol <sup>M</sup> indicates a result from multipoint analysis.

The symbol \* means that the Marshall locations were translated into LDB locations.

### Chromosome 18q

We obtained a significant two-point mod score of 4.46 in 18q21 (D18S472), using the narrowly defined shared CL phenotype, with a congruent mod score of 4.10 for BP (D18S1145) and suggestive for SZ ( $Z = 3.87$ ; D18S851). This extends our former report on chromosome 18 of a mod score of 4.03 in the same region<sup>36</sup> and increases the likelihood of a susceptibility gene shared by SZ and BP, without excluding the possibility of two distinct flanking genes for each syndrome. This chromosomal region has already yielded linkage signals for SZ and BP, as shown in Table 3 and also summarized in recent reviews.<sup>42,57</sup> Chromosome 18p11–q21 also reached nominally significant *P*-values both in the meta-analysis of BP scans by Segurado *et al*<sup>58</sup> and in that of SZ scans by Lewis *et al*.<sup>23</sup>

In conclusion, three (15q26, 16p12 and 18q12–21) of the four chromosomal regions presently showing significant linkage were related to the CL phenotype or were observed with both the SZ and BP phenotypes. This is congruent with the increasing number of genome scans in Table 3 that suggest the possibility of shared susceptibility regions and thus supports the relevance of studying in concurrence the two major psychoses.

### Suggestive linkage findings

**Chromosomes 2q and 3q** Our finding of a mod score of 2.76 at D2S298 for the CL phenotype is compared to others in Table 3, especially to Levinson *et al*'s<sup>20</sup> finding for SZ, and to the meta-analysis of Segurado *et al*<sup>58</sup> and other scans for BP. As regards chromosome 3q, our data showed two potential peaks (Figure 1), which are also compared in Table 3 to Bailer *et al*'s<sup>42</sup> genome scan of a combined (SZ + BP) phenotype whose maximum lod scores were found in 3q, close to each of our two peaks.

**Chromosome 6p22.3** The 6p22 region is the site of converging results for SZ from several genome scans. We obtained a two-point mod score of 2.82 ( $\theta = 0.10$ ) and a nearly significant evidence for heterogeneity ( $Z_{het} = 3.47$ ;  $\theta = 0.00$ ,  $\alpha = 0.66$ ,  $P = 0.06$ ) at the D6S334 locus, which were reported in our first-stage report.<sup>36</sup> Straub *et al*,<sup>59</sup> using a very broad phenotype definition including SZ and several other disorders, obtained a lod score of 3.51 at D6S296 ( $P = 0.0006$ ). Then several other scans of SZ, as well as a meta-analysis of the 6p region by Turecki *et al*,<sup>60</sup> yielded strong evidence of linkage near D6S274, very close to our peak at D6S334 (Table 3). If one considers this chromosomal region as formerly significant or replicated, as reviewed by several others,<sup>10</sup> then our mod score could be interpreted as Lander and Kruglyak<sup>43</sup> confirmatory, since it is higher than 1.9. If not, our finding nevertheless adds evidence to the likelihood of a susceptibility gene for SZ at 6p22.3. Moreover, a haplotype and a genetic variant of the dysbindin gene located in this chromosome segment

were recently found associated with SZ and SZA in unrelated probands,<sup>61</sup> a result replicated by Schwab *et al*<sup>62</sup> in another population. Our results in Figure 1 and those in Table 3 suggest that the 6p22 susceptibility region might be specific to SZ, but one major genome scan performed in the Amish population found a suggestive linkage for BP.<sup>63</sup>

**Chromosome 10** In 10p13, a suggestive mod score of 2.66 was obtained for the BP narrow phenotype in a multipoint analysis involving D10S2325 and D10S674. Nearby, we observed a mod score of 2.06 for the SZ broad phenotype. The 10p15–p11 region offered convergent suggestive findings for SZ in several large genome scans, but linkage signals were also reported for BP (Table 3). In summary, our finding adds evidence for a susceptibility region that may be shared by SZ and BP in 10p15–p11,<sup>37</sup> or perhaps of distinct and closely located genes for each syndrome.

**Chromosome 12q** We found a multipoint mod score of 3.53 with the broad BP phenotype in 12q23–q24. Several scans (Table 3) obtained linkage signals for BP near the gene locus of Darrier's disease.<sup>64</sup> Even in the presence of converging trends of findings on 12q23–q24, a conservative interpretation of our multipoint mod score of 3.53 would consider it as a suggestive rather than a confirmatory linkage.

**Chromosome 13q** A suggestive linkage ( $Z = 2.96$ ) for SZ was obtained in 13q13.3 at the D13S1491 locus. In that 6–8 cM region (Figure 1, Table 1), we also observed a mod score of 2.27 for BP (D13S325) and 2.74 for the CL phenotype (D13S1247). Badenhop *et al*<sup>65</sup> had a strong signal for BP very close to our peak (see Table 3). But there could be two peak regions in 13q13–q32: we had indeed formerly reported<sup>36</sup> a mod score of 1.65 for BP at D13S779, around 50–60 cM distal in 13q32 (Figure 1). Several scans also reported linkage signals in that latter area either for SZ or BP as shown in Table 3, and as also reviewed by others.<sup>7,9,10</sup> Berrettini's review<sup>37</sup> also suggested 13q13–q32 as a susceptibility region shared by SZ and BP. Badner and Gershon,<sup>57</sup> in their meta-analysis of SZ and BP scans, found a significant linkage for the combined SZ + BP phenotype in 13q13–q14.

It is difficult to claim that our finding in 13q13.3 is a confirmatory linkage, but our result, along with those of others, clearly suggests the presence of one or more than one susceptibility gene for SZ or BP in 13q12–q32. Only further research will elucidate the issue.

**Chromosomes 8p and 21q** The region 8p11 has been of strong interest in psychiatric genetics, especially after the identification of a risk haplotype within the neuregulin gene that was found associated with RDC SZ and SZA (see Table 3). We obtained a mod score of 1.90 ( $\theta = 0.15$ ) for the BP phenotype at D8S1110. This region has previously shown some evidence of

linkage for BP.<sup>66</sup> The meta-analysis of Badner and Gershon<sup>57</sup> suggested a trend ( $P=0.0001$ ) for the combined SZ+BP phenotype in 8p11 close to our signal for BP. As regards SZ, several genome scans shown in Table 3 reported linkage signals within a region of  $\approx 15$  cM in the vicinity of D8S1771. The 8p11 region is a good candidate for shared susceptibility<sup>37</sup> that our data do not however document.

Our linkage signal in 21q22.1 ( $Z=2.03$ ) is also of interest since it has also been the site of former findings from different genome scans (Table 3). If one considers the Aita *et al*'s<sup>67</sup> finding that achieved statistical significance for BP and the suggestive linkage of Kelsoe *et al*<sup>41</sup> and Detera-Wadleigh *et al*,<sup>68</sup> our mod score of 2.03 at D21S1893 could possibly be viewed as a confirmatory linkage according to the conservative threshold ( $Z>1.9$ ) we had *a priori* set.

#### Susceptibility regions shared by SZ and BP

At the origin of our family genetic program,<sup>6,26,27</sup> we hypothesized that susceptibility genes might be shared by the two major psychoses. This hypothesis is supported by the present findings. First, a large number of the chromosomal regions presently showing significant or suggestive linkage were either related to our CL phenotype definition combining SZ and BP, or were related to both the SZ and the BP phenotypes. This underlines the potential relevance of studying SZ and BP together, within the same study, to maximize the genetic understanding of each disorder. Second, when our findings were compared to those of published genome scans of SZ and BP, as shown in Table 3, an apparent trend pinpoints that numerous susceptibility regions, formerly thought to be specifically related to either SZ or BP, could now be recategorized as showing linkage to both BP and SZ. This was also recently noted by others.<sup>37,57</sup> Third, one of our genomewide significant findings, in 15q26 for BP, appeared to be novel. Otherwise, our strong signals beyond the significant or suggestive statistical thresholds were located in regions that may be the site of convergent findings from different genome scans performed in various populations. In sum, the field seems to be encouragingly moving, on the one hand, toward replicated convergence in some susceptibility regions and, on the other hand, toward a greater number of regions that would be shared by the two major psychoses vs others that would be specific to each. Also, the concept that several chromosomal regions may be shared by SZ and BP, and some not, may help to clarify the convergence in linkage findings.

#### Implications for the modelling of the illness complex transmission

Based on the present findings and those of others, one can posit that the genetic specificity to either SZ or BP may not come from one particular locus or gene, but from the particular combinations of a number of these susceptibility genes. Another plausible model com-

patible with our findings is one in which several susceptibility genes are shared by SZ and BP, and then, a few other modifier genes determine which of the two major psychoses will be expressed. These models are compatible with the accepted notion of an oligogenic multifactorial transmission of SZ and BP, and with the probable heterogeneity within each diagnosis. Also congruent with the latter model is the fact that a majority of the present mod scores, either significant or suggestive, were obtained with the affected-only analysis, that is, by allowing for some unaffected family members to carry the disease gene without expressing the illness. This might suggest a model in which a particular gene is necessary but not sufficient for the expression of the disorder. For instance, with this model, one would expect another gene to interact with the 6p22 gene for SZ to be expressed, or with the 16p12 gene for BP to be expressed. The potential presence of several linkage signals within the same sample paves the way for the analysis and detection of interplays or epistases.

The number of strong linkage signals observed in our sample must be considered from the perspective that we scanned the genome for two major phenotypes, SZ and BP, instead of only one as in most published scans, in addition to testing a third phenotype that combined SZ and BP. Also, the initial results we obtained from a sparse genome scan (ie the first 350 markers) were enhanced when we performed a dense genotyping with 257 additional markers in the regions that had first yielded a linkage signal. A further consideration is that few of our peaks were observed under heterogeneity but this may be due to our lack of statistical power with heterogeneity analysis. The coming genome scan of a second sample of multigenerational families including 500 members from the same population may hopefully elucidate the issue by increasing power under heterogeneity. Additional studies and the scan of this newly ascertained sample of families will hopefully contribute to answer these crucial questions and lead us to the defective genes, paving the way to a better understanding of the disease and to new treatments.

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